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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,480	08/01/2001	Charles A. Nicolette	GZ 2063.10	6547

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,480	NICOLETTE, CHARLES A.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-33 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *31-33 and 42* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/25/02, 8/5/02, 3/17/03* 8/1/01 & 8/20/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 8/1/01 is acknowledged and has been entered.

Claims 31-33 and 42 are pending.

2. Applicant's election of Group IV (claims 31-33 and newly added claim 42) in Applicant's amendment filed 8/1/01 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 31-33 and 42 are currently being examined.

3. The abstract of the disclosure is objected to because the abstract should be a single paragraph. Currently it is two paragraphs. Correction is required. See MPEP § 608.01(b).

4. The disclosure is objected to because of the following informalities:

The underlined spaces on line two of the instant specification should be deleted and amended with the appropriate US Patent No and issue date.

Appropriate corrections are required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 31-33 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed invention.

The instant claims encompass a method of inducing an immune response in any subject, comprising administering to the said subject peptides, SEQ ID NO: 1 and 3 recited in the instant claims 31 and 42, respectively, derived from gp100 melanoma antigen natural G9-209 epitope ITDQVPSFV. The specification discloses that amino acid residues at anchor positions for MHC binding and amino acid residues at CTL contract positions have been modified in the native peptide epitope ITDQVPSFV to produce the sequences FLDQVAFXV and FLFSWYAXV in order to confer tighter binding to MHC and in order to increase avidity for TCR binding (paragraph spanning pages 12 and 13). The use for the claimed peptides disclosed in the specification is generation of immune responses for treatment of melanoma, i.e., "useful as components of melanoma vaccines and to expand immune effector cells that are specific for melanoma" (page 12 at lines 20-23). The specification discloses that the two modified peptides, SEQ ID NO: 1 and 3, respectively, have been shown to sensitize Hurley R1000 TIL and INF-γ release (CTL specific for the G9-209 epitope) (page 12 at lines 23-26). The specification further discloses that the peptides of the invention can be administered alone or in conjunction with a cytokine or co-stimulatory molecule in an effective amount under conditions that induce an immune response (especially page 24 at lines 5-20). The specification discloses the term "cytokine" refers to any one of the numerous factors that exert a variety of effects on cells, for example, inducing growth or proliferation. The specification further discloses examples of cytokines which may be used alone or in combination in the practice of the instant invention (page 12 at lines 3-18). The specification discloses the term "co-stimulatory molecules" are those molecules involved in the interaction between receptor ligand pairs expressed on the surface of APC and T cells. The specification gives examples of co-stimulatory molecules (page 12 at lines 19-25).

The specification does not disclose administering the said peptides to any subject, of any HLA type, including HLA-A2, with or without administration of a cytokine and/or co-stimulatory molecule to produce a CTL response. The specification does not disclose administering the said peptides to produce an antibody response, nor that an antibody response is useful in treatment of gp100 positive melanoma in subjects.

The art recognizes that in order to be used for generating an immunogenic response with regard to generation of CTL to peptides, the subject must possess an HLA molecule to which the said peptides possess anchor residues for and can bind, and in addition, must possess CTL that can recognize the altered peptide epitopes, i.e., be cross-reactive. There is no written description in the specification of generating any type of immune response, cellular or humoral, by administering to a subject the said peptides alone or in combination with a cytokine and/or co-stimulatory molecule under any conditions. In addition, it is not sufficient to define a specificity by its principal biological activity, e.g. "co-stimulatory" or "cytokine" which in itself is ill-defined, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Adequate written description requires more than a mere statement that it is part of the invention.

7. Claims 31-33 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the claimed invention. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method of inducing an immune response in any subject of any HLA haplotype comprising administering the altered peptide ligands SEQ ID NO: 1 or SEQ ID NO: 3 with or without a cytokine and/or a co-stimulatory molecule under conditions that induce an immune response to the said peptides.

The instant claims encompass a method of inducing an immune response in any subject, including an HLA-A2 positive subject, comprising administering to a subject peptides derived from gp100 melanoma antigen natural G9-209 epitope ITDQVPSFV wherein amino acid residues at anchor positions for MHC binding and amino acid residues at CTL contract positions have been modified to produce the sequences FLDQVAFXV and FLFSWYAXV in order to confer tighter binding to MHC and in order to increase avidity for TCR binding (paragraph spanning pages 12 and 13). The use for the claimed peptides disclosed in the specification is generation of immune responses for treatment of melanoma, i.e., "useful as components of melanoma vaccines and to expand immune effector cells that are specific for melanoma) (page 12 at lines 20-23). The specification discloses that the two modified peptides, SEQ ID NO: 1 and 3, respectively, have been shown to sensitize Hurley R1000 TIL and INF-γ release (CTL specific for the G9-209 epitope) (page 12 at lines 23-26). The specification further discloses that the peptides of the invention can be administered alone or in conjunction with a cytokine or co-stimulatory molecule in an effective amount under conditions that induce an immune response (especially page 24 at lines 5-20). The specification further discloses that the peptides of the invention can be administered alone or in conjunction with a cytokine or co-stimulatory molecule in an effective amount under conditions that induce an immune response (especially page 24 at lines 5-20). The specification discloses the term "cytokine" refers to any one of the numerous factors that exert a variety of effects on cells, for example, inducing growth or proliferation. The specification further discloses examples of cytokines which may be used alone or in combination in the practice of the instant invention (page 12 at lines 3-18). The specification discloses the term "co-stimulatory molecules" are those molecules involved in the interaction between receptor ligand pairs expressed on the surface of APC and T cells. The specification gives examples of co-stimulatory molecules (page 12 at lines 19-25).

The specification does not disclose administering the said peptides to any subject, of any HLA type, including HLA-A2, to produce a CTL response, nor to produce an antibody response, nor to treat a subject with melanoma. The specification does not disclose administering the said peptides to produce an antibody response, nor that an antibody response is useful in treatment of melanoma in gp100 positive, HLA-A2 positive melanoma subjects.

The art recognizes that in order to be used for generating an immunogenic response with respect to generation of CTL to peptides, the subject must possess an HLA molecule to which the said peptides possess anchor residues for and can bind, and in addition, must possess CTL that can recognize the altered peptide epitopes, i.e., be cross-reactive. Evidentiary reference Clay et al (J. Immunol. 1999, 162: 1749-1755) teach modification of the G9-209 epitope peptide at the position 2 anchor residue to Met, Ile or Leu increases the peptide binding affinity to HLA-A2, the G9-209 2M modified peptide being the most effective for generating CTL that recognize the parent G9-209 peptide. Clay et al further teach that vaccination of HLA-A2 positive melanoma patients with the G9-209 2M peptide led to a significant increase in antigen specific precursors (CTLp), with activity that could be elicited in vitro against the native G9-209 peptide, however, despite the said increase in frequency of CTLp, no objective clinical responses were observed when patients were treated with peptide alone (especially columns 1 and 2 on page 1749). Clay et al teach that administration of the G9-209 2M peptide alone expanded low avidity G9-209 reactive CTL in peripheral blood, but that melanoma patients treated with the G9-209 2M peptide in combination with IL-2 had a higher response rate for anti-tumor responses than those treated with either the peptide or IL-2 alone. Clay et al teach that the best strategy may be to expand individual tumor reactive cloids in vitro and use them individually or in pools in adoptive immunotherapy protocols to treat gp100 bearing HLA-A2 positive melanoma patients (especially page 1754 at the last paragraph). Evidentiary reference Dudley et al (J. Immunotherapy, 22(4): 288-298) teach that peptide immunization is an attractive approach to tumor immunotherapy, but the technique is still largely untried, and many questions remain to be answered before this treatment can reach its full potential. Dudley et al further teach that it is not known if a minimal CTL epitope introduced into a patient can provoke the same magnitude of immune response as a native antigen (especially last paragraph on page 295). Dudley et al teach that the ability to generate CTL reactive to high peptide concentrations may not imply that those CTL will recognize potentially low concentrations of antigen on tumor, that CTL avidity and its role in tumor evaluation needs to be further evaluated in preclinical models and in clinical trials involving peptide immunization (especially page 297 at lines 2-8). Dudley et al teach an alternate strategy in generating high avidity cells for adoptive transfer (especially last paragraph on page 297).

There is no guidance in the specification as to what conditions of administration result in "conditions that induce an immune response to the polypeptide" in any subject of any HLA type by administration of the claimed peptides with or without a cytokine and/or a costimulatory molecule. It is not sufficient to define a specificity by its principal biological activity, e.g. costimulatory which in itself is ill-defined, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. The scope of the claims must bear a reasonable correlation with the scope of enablement. Because of this lack of guidance, and unpredictability in the art, extended experimentation that would be required to determine in which subjects and under what conditions a useful immune response could be produced. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 31-33 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31 and 42 are indefinite in the recitation of "polypeptide" in line 4 because it is not clear what is meant. Line 2 of the said claims recite "peptide".

10. The references crossed out in the Form 1449 filed 8/5/2002 have not been considered because they are duplicate entries of those contained in the Form 1449 filed 8/1/01. The reference 5 has not been considered because no translation has been provided for the French language document.

11. The NPL references crossed out in the Form 1449 filed 8/20/02 have not been considered because they were not provided. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

12. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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